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Stereoselective Synthesis of Alkyl α-D-Glucopyranosides

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Glycosylation of β-D-glucosyl *N*-allyl thiocarbamates with alcohols using bromine as activator proceeded under mild conditions in a highly stereoselective fashion to afford the corresponding α-glucosides in high yields. Hindered tertiary alcohols can be also used as glycosyl donors.

Key words: glycosides, glycosylation, thiocarbamates

Preparation of anomerically pure glycosides is one of the most characteristic and important problems in carbohydrate chemistry [1]. While the synthesis of 1,2-trans glycosides is effectively performed using so-called neighbouring group participation by introduction of an acyloxy group at the C-2 position of glycosyl donor [1], there are no such general synthetic procedures available for construction of 1,2-cis glycosides. A number of new stereoselective 1,2-cis glycosylation methods have been developed recently [1], but they often fail when applied to glycosylation of hindered and acid sensitive alcohols [2].

Fraser-Reid has developed a glycosylation method, based on electrophile-induced cyclization of pentenyl glycosides [3]. Addition of electrophile to a double bond followed by intramolecular alkylation of an oxygen atom causes that heterocycle formed this way acts as an efficient leaving group and the remaining carboxonium ion reacts with glycosyl acceptor to give the glycoside [4].

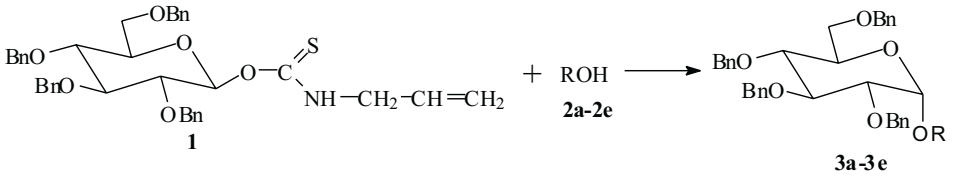
It is well documented that the soft sulfur atom is more prone to alkylation than hard oxygen atom. This stimulated development of a glycosylation method based on electrophile-induced cyclization of glycosyl N-allyl thiocarbamates [5].

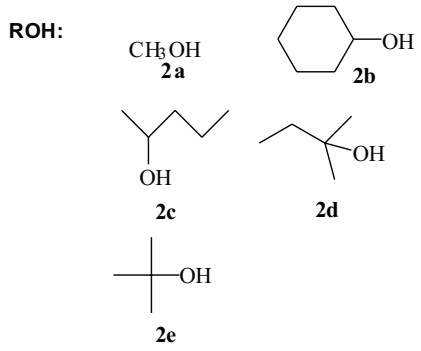
As a part of our program of the synthesis of complex glycosides, we therein report on a stereoselective 1,2-cis glucosylation method using *O*-glucosyl *N*-allyl thiocarbamate as a novel glycosyl donor.

RESULTS AND DISCUSSION

The starting tetra-*O*-benzyl-β-D-glucopyranosyl *N*-allyl thiocarbamate (**1**) was obtained from anomerically unprotected tetra-*O*-benzyl-D-glucopyranose and commercially available *N*-allyl isothiocyanate [6]. The glycosyl *N*-allyl thiocarbamates are stable and can be stored for at least a month without decomposition.

Scheme 1





Initially, glycosylation of **1** with cyclohexyl alcohol (**2b**) using different activators: Br_2, $Hg(OAc)_2$, $Hg(CF_3CO_2)_2$ was examined.

Results summarized in Table 1 clearly show that both the yield and α-stereoselectivity of glycosidation of **1** using bromine as promoter are good.

Table 1. Glycosylation of **2b** by different promoters[a].

entry	activation	base	solvent	time (min)	yield[b] (%) of α-glucoside
1	Br_2	K_2CO_3	$(CH_2Cl)_2$	10	75
2	Br_2	$NaHCO_3$/DBU	$(CH_2Cl)_2$	10	82
3	$Hg(CF_3COO)_2 - LiClO_4$	–	$(CH_2Cl)_2$/DMF (20:1, v/v)	15	76
5	$Br_2 - LiClO_4$	$NaHCO_3$	$(CH_2Cl)_2$/DMF (20:1, v/v)	10	69

[a]Reactions were carried out with 2 equiv. of alcohol **2b**. [b]Isolated yields after column chromatography.

Thus, glycosylation of **1** utilizing Br_2 in $(CH_2Cl)_2$/DMF at r.t. for 10 min proceeded effectively to produce the corresponding glucoside in good yield, especially in the presence of DBU as acceptor of an acid. Next our attention moved to the solvent effect in this novel glycosidation. Therefore, we carried out glycosidation of **1** and **2b** using bromine in various solvents of different in polarity: $(CH_2Cl)_2$, diethyl ether, THF, CH_3CN, DMF and a mixture $(CH_2Cl)_2$/DMF.

From the results shown in Table 2, ethylene chloride was found to be the best solvent with respect to both chemical yield and stereoselectivity. The chemical yield was low when more polar diethyl ether, CH_3CN, or a mixture $(CH_2Cl)_2$/DMF were used as the solvents (entries 2, 3, 4 in Table 2).

Glycosidation did not occur in THF and DMF. Analysis of the mechanism of this reaction [4,5] led to the conclusion that the intermediate carboxonium ion would be efficiently stabilized by anions of strong acids. Considering a series of experiments, the influence of lithium salts of inorganic and organic acids was examined. Results in Table 3 showed that addition of salt improved the yield of the glycoside. High α-selectivity and good yields were observed, especially in the presence of lithium triflate (Table 3).

Table 2. Glucosylation **2b** in several solvents[a].

entry	solvent	time (min)	yield (%)[b]	α/β[c]
1	$(CH_2Cl)_2$	10	75	only α
2	$(CH_2Cl)_2$/DMF (20:1; v/v)	10	69	only α
3	Et_2O	15	65	only α
4	CH_3CN	15	50	α and several unidentified products
5	DMF	30	–	no product
6	THF	30	–	no product

[a]All reactions were carried out with 2 equiv. of **2b** and 1.0 equiv. of $NaHCO_3$. [b]Isolated yields after column chromatography. [c]α/β ratios were determined by ^{1}H-NMR (300 MHz) spectroscopy or by isolation of pure isomer(s).

Table 3. Influence of salts on the glycosidation[a] reaction.

entry	salts	yield[b] (%) of α-glucoside
1	$LiSO_3CF_3/NaHCO_3$	89
2	$LiClO_4/NaHCO_3$	69
3	$LiPF_6/NaHCO_3$	70

[a]All reactions were carried out with 2 equiv. of **2b** and 1 equiv. of salts. [b]Isolated yields after column chromatography.

Basing on these results, bromine was selected as an activator in the general procedure of synthesis of alkyl α-D-glucosides. Reaction of **1** with primary (**2a**), secondary (**2b**, **2c**) and tertiary (**2d**, **2e**) alcohols was performed in ethylene chloride/DMF mixture as a solvent containing lithium triflate or perchlorate. It is noteworthy that very reactive primary alcohol (methyl alcohol) as well as sterically hindered less reactive tertiary alcohols (t-butyl alcohol, t-amyl alcohol) are stereo-selectively glycosylated with high yields. Composition of the products of glucosylation of 2-pentanol (racemic mixture) might be usually determined by NMR [7]. The shift to the higher field of anomeric carbon atom in glycosides derivatives of secondary alcohols with *R* configuration was observed. We have found two signals of anomeric carbon (δ = 94.18 ppm, δ = 93.53 ppm) and two H-1 signals (δ = 4.91, $J_{1,2}$ = 1.50 Hz and δ = 4.92,

$J_{1,2}$ = 1.50 Hz) of practically the same intensity in the spectra of 2-pentyl glucoside, indicating that an equimolar mixture of diastereoisomeric 2-pentyl α-D-glucosides is formed in this reaction.

Characteristic features of the present methodology are:

- The glycosyl donor can be prepared very easily and is stable.
- Required activators are non-toxic, and salts of silver or mercury are not necessary.
- Mildness of the reaction conditions is noteworthy; acid-sensitive alcohols did not undergo any decomposition.
- It was confirmed that formed glycosides did not undergo epimerization under the reaction conditions.

In summary, we demonstrated that *O*-glucosyl *N*-allyl thiocarbamate can serve as an effective glycosyl donor in synthetic carbohydrate chemistry. We are currently applying this methodology to the synthesis of oligosaccharides.

EXPERIMENTAL

General methods. Optical rotations were measured with a Perkin Elmer 141 polarimeter using sodium lamp (589 nm) at room temperature. ^{1}H NMR spectra were recorded with a Varian 300 MHz spectrometer for solutions in $CDCl_3$ (internal TMS). TLC was performed on percoated plates of silica gel $60F_{254}$ (Merck), using hexane/ethyl acetate (3:1 v/v) and the spots were visualized by spraying with sulfuric acid. Chromatographic purification was performed on silica gel 60 (Merck) 0.063–0.2 mm. All solutions were concentrated under diminished pressure at 40°C. Organic solutions were dried over anh. $MgSO_4$.

Starting materials. 2,3,4,6-Tetra-*O*-benzyl-1-*O*-[*N*-allyl thiocarbamoylo]-β-D-glucopyranose was prepared according to [6].

General procedure. Sugar **1** (1 mmol) was dissolved in the corresponding solvent [mixture of $(CH_2Cl)_2$/DMF (20:1 v/v, 8/0.4 ml), Et_2O, CH_3CN, DMF, THF for **2b**] containing micronised molecular sieves 4 Å (50 mg) and vigorously stirred at room temperature for 10 minutes. Alcohol **2a**–**2e** (2 mmol), $LiClO_4$ (or $LiSO_3CF_3$) (1 mmol), $NaHCO_3$ (1 mmol) were added and after 20 minutes this mixture was cooled down (–25°C) and bromine (1 mmol) was added. The reaction was complete (TLC, 3:1 hexane/ethyl acetate) in 10 minutes. The mixture was filtered, concentrated and the crude product was purified by column chromatography (hexane/ethyl acetate 5:1 and 3:1 v/v).

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (3a), (74% for $LiClO_4$), syrup, $[\alpha]_D^{20}$ 21.8° (c 1.0, $CHCl_3$) {lit.[8] $[\alpha]_D^{20}$ 20.9° (c 0.7, $CHCl_3$)}.

Cyclohexyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (3b), (69% for $LiClO_4$) (89% for LiTf), syrup, $[\alpha]_D^{20}$ 41.8° (c 1, $CHCl_3$) {lit. [9] $[\alpha]_D^{20}$ 42.0° (c 1, $CHCl_3$)}, ^{1}H NMR δ: 1.10–2.00 (m, 10H, cyclohexyl), 3.55 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.60–3.68 (m, 3H, H-4, H-6′, H-cyclohexyl), 3.74 (dd, 1H, $J_{6,6'}$ = 10.5 Hz, $J_{6,5}$ = 3.6 Hz, H-6), 3.88 (m, 1H, H-5), 4.00 (t, 1H, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 4.46; 4.61 (AB, 2H, J = 12.2 Hz, Ph$\underline{CH}_2$), 4.47; 4.83 (AB, 2H, J = 10.7 Hz, Ph$\underline{CH}_2$), 4.65; 4.74 (AB, 2H, J = 11.4 Hz, Ph$\underline{CH}_2$), 4.93 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.81; 5.00 (AB, 2H, J = 10.7 Hz, Ph$\underline{CH}_2$), 7.10–7.40 (m, 20H, Ph).

(*R*, *S*) (2-Pentyl) 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (3c), (65% for $LiClO_4$), syrup, ^{1}H NMR δ: 0.80–1.00 (m, 6H), 1.10–1.80 (m, 16H), 3.40–4.20 (m, 12H), 4.41–4.88 (m, 16H), 4.91 (d, 1H, $J_{1,2}$ = 1.50 Hz), 4.92, (d, 1H, $J_{1,2}$ = 1.50 Hz), 7.15–7.45 (m, 40H, Ph), ^{13}C NMR δ: 139.0–137.5 (aromatic), 128.8–127.2 (aromatic), 94.18 (C-1 (*S*)), 93.53 (C-1 (*R*)), 82.19, 82.11, 79.89, 79.81, 77.98, 77.94, 75.70 (Ph-$\underline{C}H_2$-), 75.67 (Ph-$\underline{C}H_2$-), 74.98 (Ph-$\underline{C}H_2$-), 74.81 (Ph-$\underline{C}H_2$-), 74.57 (Ph-$\underline{C}H_2$-), 73.48 (Ph-$\underline{C}H_2$-), 73.38 (Ph-$\underline{C}H_2$-), 70.32 ($CH_3\underline{C}H$-O-), 70.18 ($CH_3\underline{C}H$-O-), 68.59, 67.74, 39.45 (-CH-$\underline{C}H_2$-CH_2-), 38.35 (-CH-$\underline{C}H_2$-CH_2-), 21.18 ($\underline{C}H_3$-CH-), 19.32 ($\underline{C}H_3$-CH-), 18.90 ($CH_3\underline{C}H_2$-), 18.60 (CH_3-$\underline{C}H_2$-), 14.20 ($\underline{C}H_3$-CH_2-), 14.05 ($\underline{C}H_3$-CH_2-). Anal. Calcd. for $C_{39}H_{46}O_6$: C, 76.69; H, 7.59. Found: C, 76.71; H, 7.61.

***tert*-Amyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (3d)**, (55% for $LiClO_4$), (88% for LiTfl), syrup, $[\alpha]_D^{20}$ 42.4° (c 1, $CHCl_3$), ^{1}H NMR δ: 0.95 (m, 3H), 1.00–1.60 (m, 6H), 1.70 (m, 2H), 3.55 (dd, 1H, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.60–3.68 (m, 2H, H-4, H-6′), 3.74 (dd, 1H, $J_{6,6'}$ = 10.5 Hz, $J_{6,5}$ = 3.6 Hz, H-6), 3.88 (m, 1H, H-5), 4.00 (t, 1H, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 4.46; 4.61 (AB, 2H, J = 12.2 Hz, Ph$\underline{CH_2}$), 4.47; 4.83 (AB, 2H, J = 10.7 Hz, Ph$\underline{CH_2}$), 4.65; 4.74 (AB, 2H, J = 11.4 Hz, Ph$\underline{CH_2}$), 4.93 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.81; 5.00 (AB, 2H, J = 10.7 Hz, Ph$\underline{CH_2}$), 7.10–7.40 (m, 20H, Ph). Anal. Calcd. for $C_{39}H_{46}O_6$: C, 76.69; H, 7.59. Found: C, 76.72; H, 7.62.

***tert*-Butyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (3e)**, (60% for $LiClO_4$), (87.5% for LiTfl), syrup, $[\alpha]_D^{20}$ 41.0° (c 0.59, $CHCl_3$) {lit. [10] $[\alpha]_D^{20}$ 41.5° (c 0.61, CH_3Cl)}, ^{1}H NMR δ: 1.25 (s, 9H), 3.55 (dd, 1H, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 9.4 Hz, H-2), 3.61–3.69 (m, 2H, H-4, H-6′), 3.75 (dd, 1H, $J_{6,6'}$ = 10.6 Hz, $J_{6,5}$ = 3.7 Hz, H-6), 3.90 (m, 1H, H-5), 4.15 (t, 1H, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 4.49; 4.70 (AB, 2H, J = 12.2 Hz, Ph$\underline{CH_2}$), 4.49; 4.81 (AB, 2H, J = 10.6 Hz, Ph$\underline{CH_2}$), 4.61; 4.98 (AB, 2H, J = 10.5 Hz, Ph$\underline{CH_2}$), 4.72; 4.83 (AB, 2H, J = 11.7 Hz, Ph$\underline{CH_2}$), 5.12 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 7.11–7.41 (m, 20H, Ph).

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